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Targeting HER-2 Signaling Network: Implication in Radiation Response

In Ah Kim

*Department of Radiation Oncology, Seoul National University,
Republic of Korea*

1. Introduction

The Human Epidermal Growth Factor Receptor 2 (HER2) oncogene encodes a 185 kDa type I tyrosine kinase receptor that is a member of the epidermal growth factor receptor (EGFR) family including HER1, HER2, HER3 and HER4 (Yarden & Sliwkowski, 2001). Overexpression of HER2 is observed in 25-30% of human breast cancers and is associated with poor prognosis (Slamon et al., 1989; Cooke et al., 2001).

HER2 overexpression activates multiple signaling pathways and promotes tumor growth, proliferation, and survival. The underlying mechanism for this action was elucidated by several studies involving critical components of the HER2 regulated pathway including phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) cascades (Huang & Lau, 1999). The most widely used anti-HER2 therapy is the recombinant humanized antibody trastuzumab, which represented the proof of principle for the targeting of tyrosine kinase receptors in breast cancer. Trastuzumab exerts its antitumor activity by induction of receptor degradation (Klapper et al., 2000), prevention of HER2 ectodomain cleavage (Molina et al., 2001), inhibition of HER2 kinase signal transduction via antibody-dependent cellular cytotoxicity (Clynes et al., 2000) and inhibition of angiogenesis (Izumi et al., 2002). Trastuzumab has been approved as a front-line therapy for HER2-positive breast cancer patients in both adjuvant and metastatic settings (Hudis, 2007), however, trastuzumab fails in 50-70% of HER2-positive patients (Vogel et al., 2002; Slamon et al., 2001).

Radiotherapy is employed as an integral part of the current comprehensive breast cancer treatment regimen, and may be used to eradicate remaining cancer cells in the breast, chest wall, or axilla after surgery or to reduce the size of an advanced tumor before surgery. A series of studies have shown the evidences regarding the potential value of targeting HER-2 signaling to enhance the anti-tumor activity of ionizing radiation. However, therapeutic resistance, resulting from several factors including activation of downstream pathway or alternative survival pathways, as well as molecular resistance mechanisms, has been emerged as an important issue in clinic.

We have been trying to identify the component(s) implicated in radiation response in HER-2 signaling network and also screening the useful approaches to overcome therapeutic resistance such as targeting downstream effectors, ligand-independent modulation via heat shock protein 90 (HSP90) inhibition and epigenetic modulation of HER-2 signaling via inhibition of histone deacetylases (HDACs). The efficacy and clinical relevance of each strategy and the diverse mechanisms of radiosensitization will be discussed.

2. Targeting downstream signaling

Overamplification of the HER2 gene results in formation of a ligand-independent HER2 homodimer that is able to initiate downstream signaling cascades such as the PI3K and MAPK pathways (Pinkas-Kramarski et al., 1996). While the inhibition of MEK-ERK signaling did not increase the radiosensitivity of SKBR3 breast cancer cells exhibiting overamplification of HER2, selective inhibition of PI3K-Akt-mTOR pathway components radiosensitized SKBR3 cells (No et al., 2009). Loss of PTEN (phosphatase and tensin homolog deleted one chromosome ten) expression results in trastuzumab resistance, and PI3K inhibitors restore trastuzumab sensitivity in PTEN-deficient cells (Nagata et al., 2004). Berns et al. recently provided strong confirmatory evidence that activation of the PI3K pathway through loss of the tumor suppressor PTEN or through oncogenic stimulation of PI3K can mediate trastuzumab resistance (Berns et al., 2007).

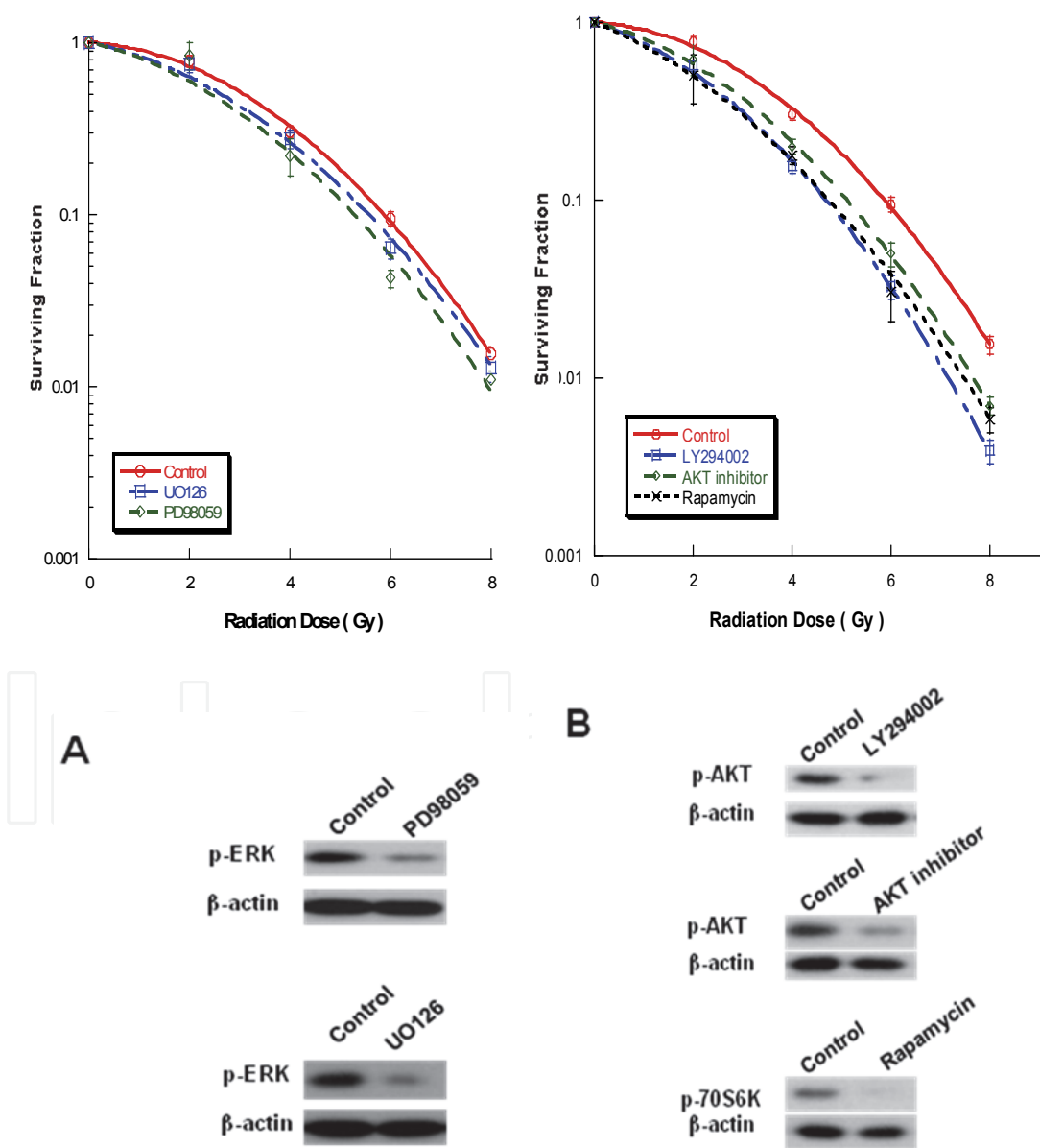


Fig. 1. Targeting downstream of HER-2 signaling (No et al, 2009).

2.1 Targeting PI3K-AKT-mTOR pathway

2.1.1 Targeting PI3K

PI3K, a heterodimer consisting of p85 regulatory subunit and a 110 catalytic subunit, plays a central role in growth regulation and tumorigenesis. It generates specific inositol lipids (PIP2, PIP3) that have been implicated in the regulation of cell proliferation, differentiation, survival, and angiogenesis (Engelman et al., 2006). Recently, several groups reported that 18-40% of human breast cancers harbor somatic mutations of PI3K (Levin et al., 2005), resulting in constitutive activation of PI3K signaling. PTEN inhibits PI3K by dephosphorylation of the second messenger PIP3. PTEN appears to be controlled by down-regulation of gene expression and genetic alterations of this tumor suppressor are found in a moderate proportion of breast cancers.

2.1.2 Targeting AKT

AKT/PKB is a serine/threonine kinase that plays an important role in cancer progression and cell survival and is activated in a PI3K-dependent manner by a variety of stimuli through growth factor receptors. Among the specific AKT family members, increased AKT1 activity was reported in 40% of breast cancers (Manning et al., 2007). We previously showed that inhibition of AKT1 using RNAi increased radiosensitivity of EGFR- or Ras-activated cell lines (Kim et al., 2005) and the other study showed that AKT inhibitor (API) or AKT1 siRNA inhibited repair of DNA double strand breaks (DSBs) in EGFR-activated lung cancer cell lines as measured by the γ H2AX foci assay (Toulany et al., 2008). SKBR3 breast cancer cells having activated HER-2 signaling also showed similar findings (Figure 3, No et al., 2009).

2.1.3 Targeting m-TOR

The mammalian target of rapamycin (mTOR) is an important downstream component of the PI3K-AKT signaling pathway. mTOR inhibitors can effectively block the pro-growth, pro-proliferative, and pro-survival actions of mTOR by inactivating its downstream effectors such as p70S6 kinase and 4E-binding protein1 and decreasing protein synthesis (Shaw et al., 2006; Guertin & Sabatini, 2007). mTOR presents an attractive target in the pathway because its inhibition could avoid possible side effects associated with inhibition of upstream PI3K/AKT signaling molecules with broader function. We previously showed that the radiosensitizing effect of Rapamycin is related to inhibition of DNA damage repair, as demonstrated by the γ H2AX foci assay using SKBR3 cells (Fig. 2, No et al., 2009). Recent report showed that RAD001 attenuated prosurvival AKT/mTOR signaling and increased radiation sensitivity of MDA-MB-231 breast cancer cells (Albert et al., 2006).

2.1.4 Targeting class I PI3K and m-TOR

One of the reasonable approaches would be the targeting more than one component of tumor specific signaling that less affect normal cell survival. Inhibition of PI3K using LY294002 lacks specificity and has shown unacceptable toxicities in preclinical studies. Previous study showed that specific inhibition of class I PI3K using RNAi enhanced the radiosensitivity of tumor cells having activated PI3K signaling resulting from overexpression of EGFR or mutation of RAS oncogene (Kim et al., 2005). The PI103 is known as a dual inhibitor which targets class I PI3K and mTOR signaling which reduce radiation survival of tumor cells with AKT activation. (Prevo et al., 2008). PI103 effectively radiosensitized SKBR3 cells with activated HER2 signaling and this sensitizing effect

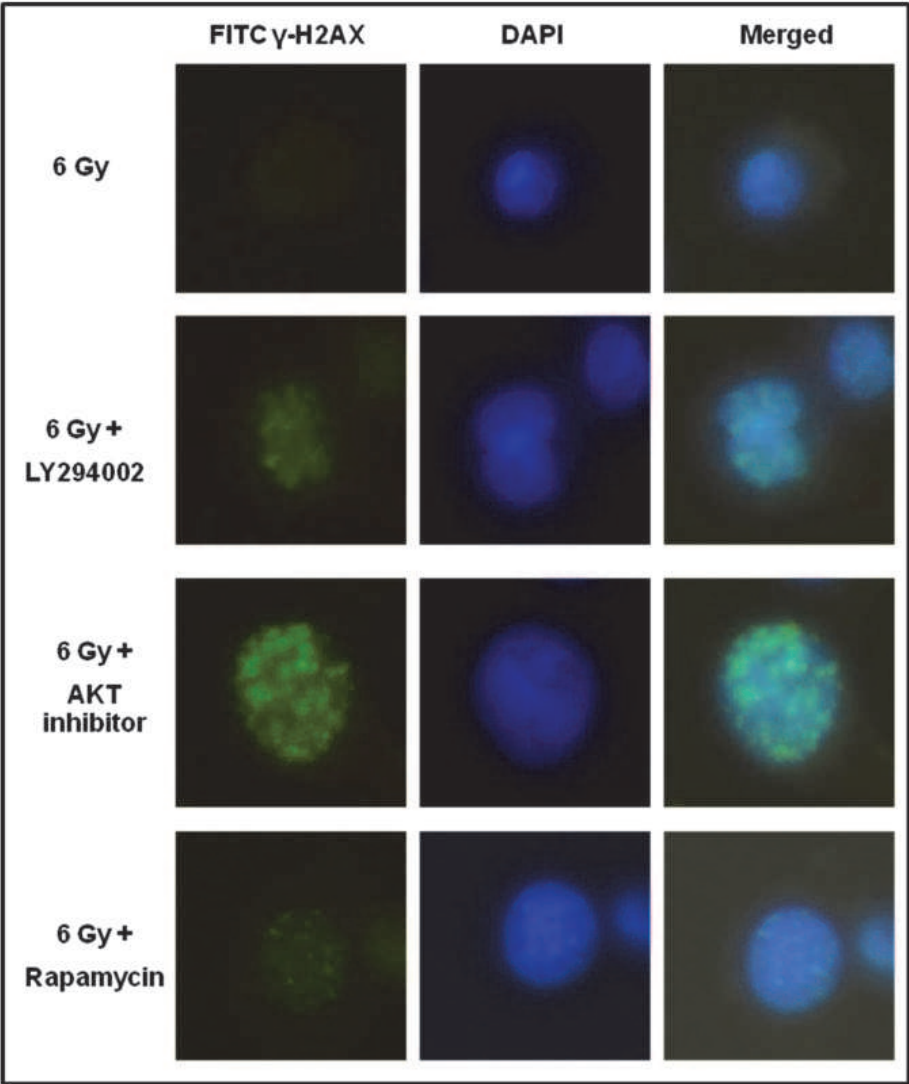


Fig. 2. Persistent γH2AX foci following orradiation by selective inhibition of PI3K-AKT-mTOR signalling (No et al., 2009).

was associated with prolongation of γH2AX foci following irradiation. Decreased phosphorylation of DNA-PKs by pretreatment of inhibitors targeting PI3K-AKT indicated that the functional requirement of PI3K-AKT pathway in regulation of DNA repair following radiation (Fig.3 & 4, No et al., 2009). While apoptosis was the major mode of cell death when the cells were pretreated with LY294002 or AKT inhibitor VIII, cells were pretreated by Rapamycin or PI103 showed the mixed mode of cell death including autophagy (Fig. 5, No et al., 2009).

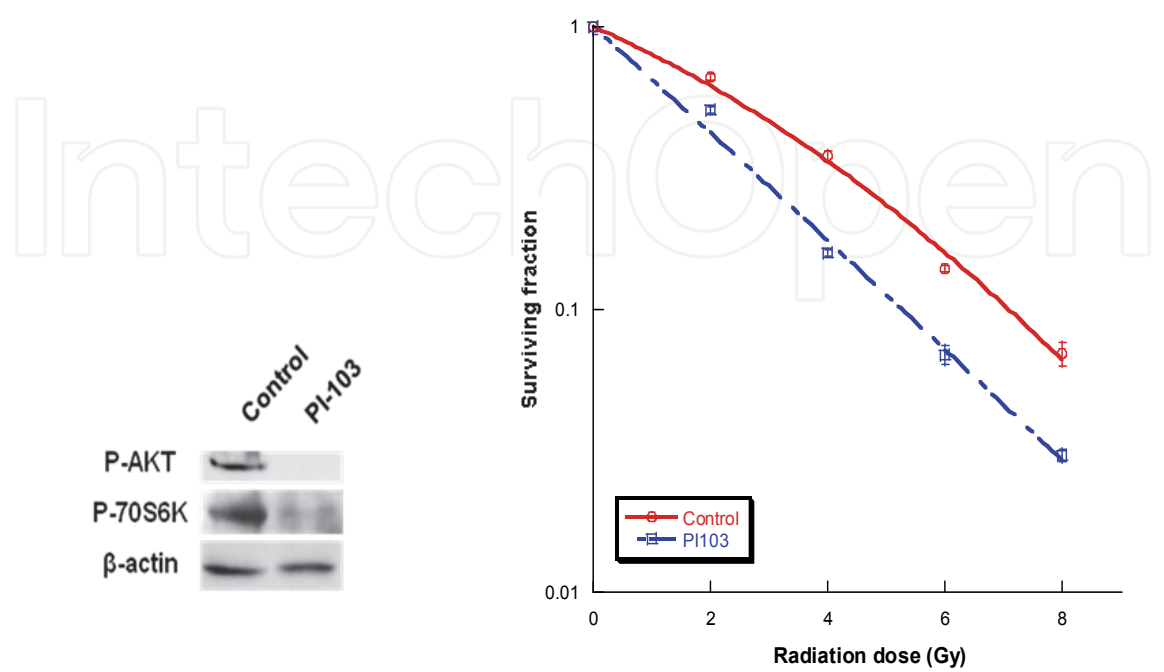


Fig. 3. Targeting Class I PI3K and m-TOR using dual inhibitor (No et al., 2009).

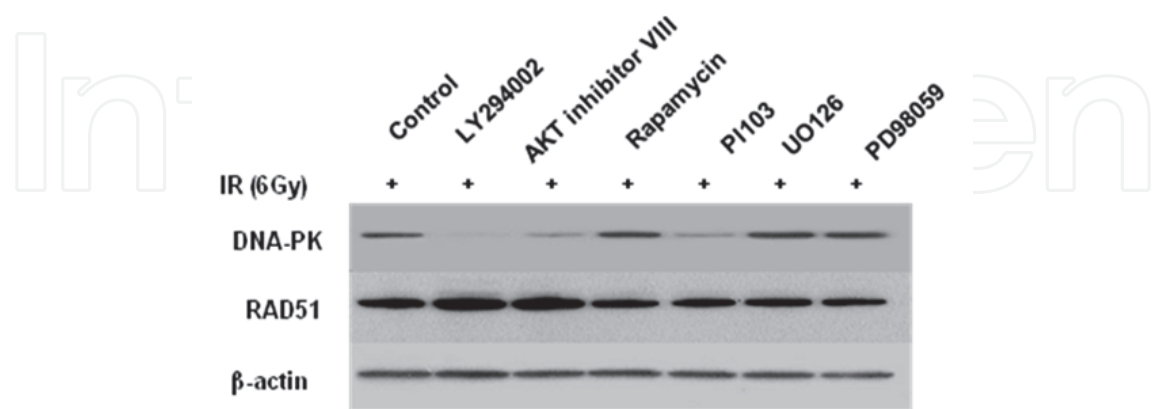


Fig. 4. Targeting Class I PI3K-Akt down-regulated DNA-PK expression (No et al., 2009).

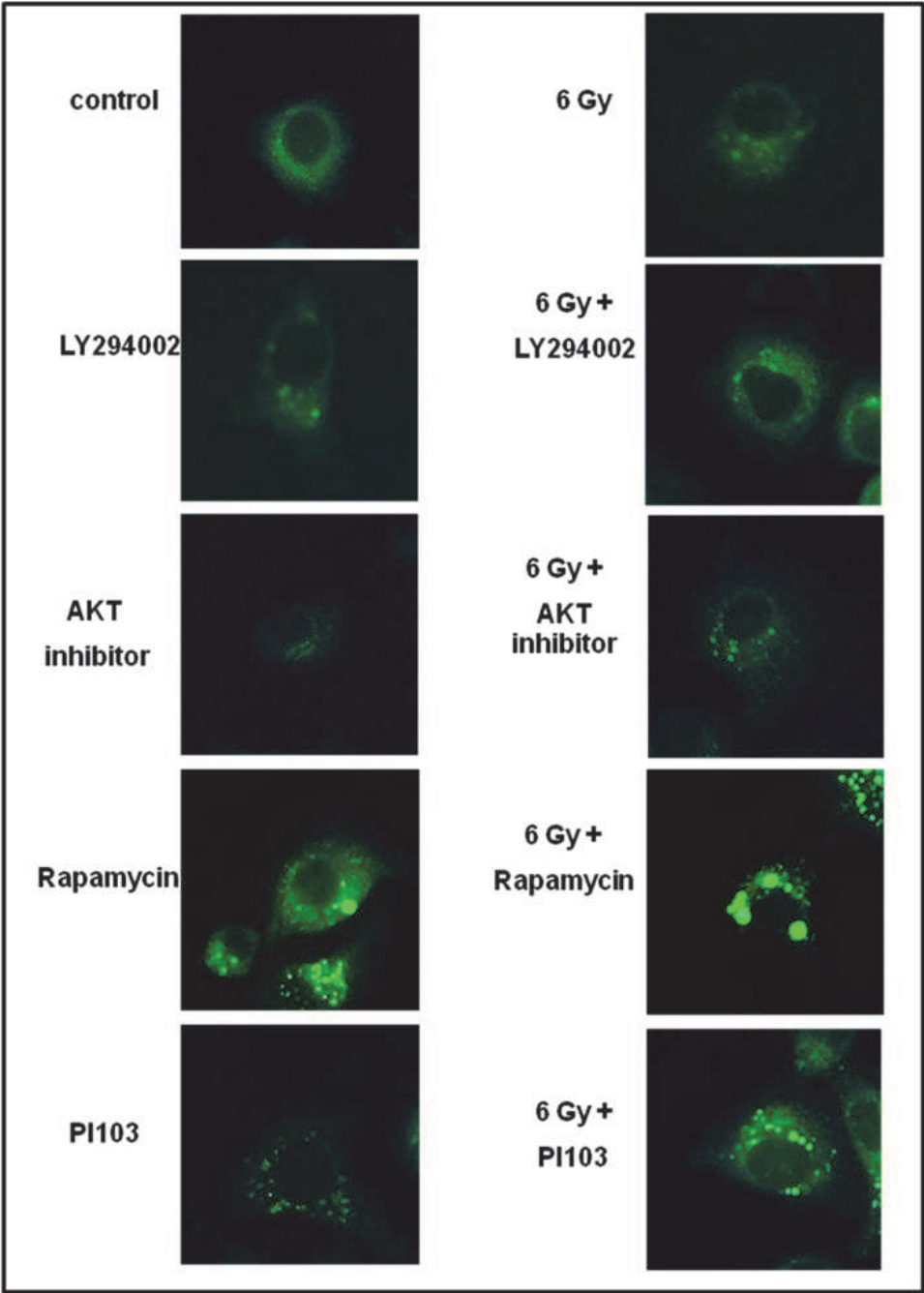


Fig. 5. Rapamycin and PI103 induced autophagy following irradiation. (No et al., 2009).

3. Ligand-independent modulation of HER-2 signaling: HSP90 inhibition

The majority of breast cancers involve multiple molecular abnormalities that are likely to be involved in malignant progression. It is possible that several different molecules from diverse pathways have synergistic properties that promote malignant relapse or metastasis. In that situation, HSP90 could be a pivotal key molecule, as its chaperone function ensures the correct conformation, activity, intracellular localization, and proteolytic turnover of a range of proteins involved in cell growth, differentiation, and survival (Neckers et al., 2003). This molecular chaperon is essential for the stability and function of many oncogenic client

proteins, which contributes to the hallmark trait of cancers such as ER, HER-2, and AKT (Powers & Workman, 2006). The inhibition of multiple targets through the abrogation of HSP90 could be more effective in the management of breast cancers, since its inhibition counteracts multiple oncogenic molecules and prosurvival signaling pathways at the same time.

Additional data supports the identification of HSP90 as an important molecular target relevant to breast cancers. HER2, which is associated with poor prognosis in breast cancer, is one of the most important client proteins of HSP90, and HSP90 inhibitors have shown antitumor activity in a HER2-driven xenograft model (Kamal et al, 2003). Additionally, HSP90 inhibitors bind selectively to HSP90 in cancerous cells versus normal cells (Munster et al, 2001). Breast cancer cells resistant to conventional chemotherapy, radiation therapy, and trastuzumab, are known to involve the PI3K signaling pathway. The key molecule of this pathway, AKT, is also an important client protein of HSP90.

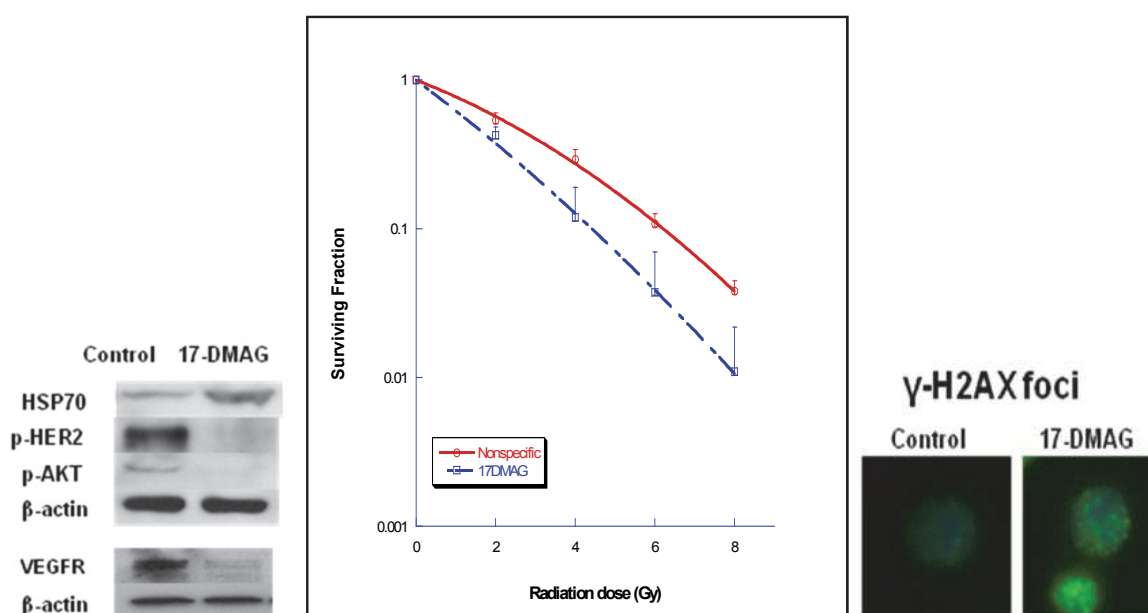


Fig. 6. 17-DMAG, a HSP90 inhibitor radiosensitized SKBR-3 cells with HER-2 overexpression.

A HSP90 inhibitor, 17-(allylamino)-17-demethoxy-geldanamycin (17-AAG) downregulated HER2 in trastuzumab-resistant breast cancer cells (Zsebik et al., 2006). We also have observed that 17-DMAG, led to downregulation of HER-2 and p-AKT, and radiosensitized HER-2 activated breast cancer cells. This radiosensitizing effect was associated with persistence of γ H2AX foci following irradiation (Figure 6, unpublished data).

Our previous immunohistochemical study using tissue samples from 212 patients who underwent surgical resection for primary invasive breast cancer, have shown that expression of HSP90 from invasive breast cancer was associated with an increased risk of early recurrence (Fig. 7, Song et al., 2010). Co-expression of HSP90 and PI3K or expression of HSP90 in combination with the loss of PTEN was significantly associated with RFS especially in the patient group having HER-2 overexpression (Fig.8, Song et al., 2010). This study provides direct evidence that the expression of HSP90 predicts early relapse in patients with invasive breast cancers and validates the significance of HSP90 as a clinically significant therapeutic target.

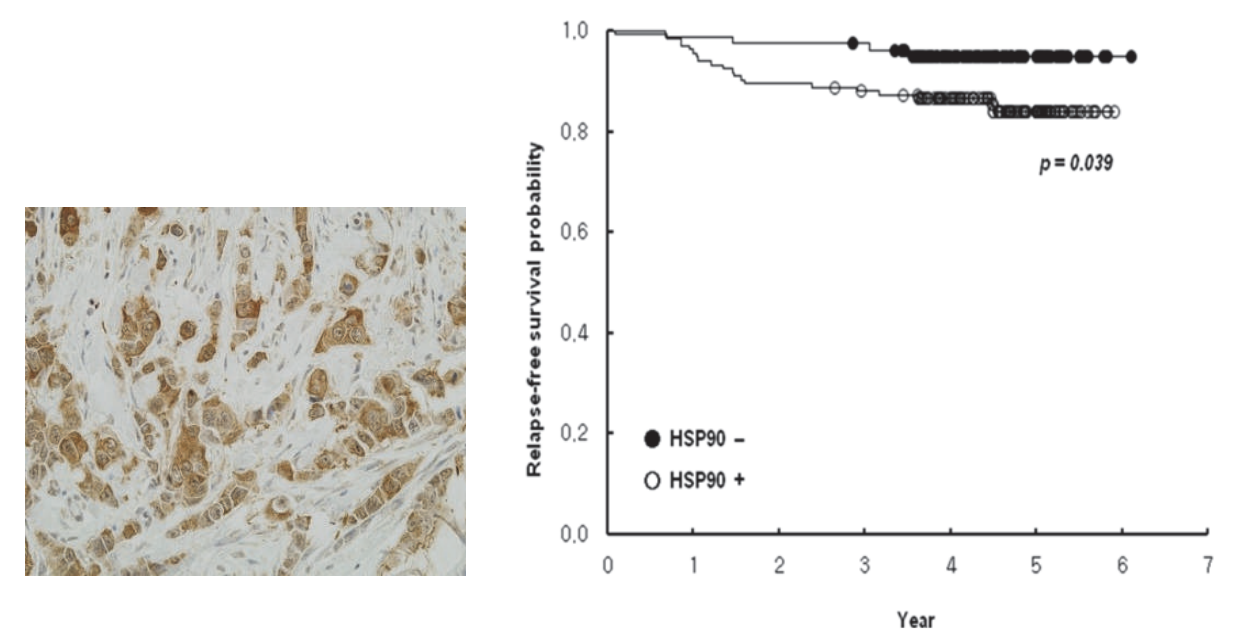


Fig. 7. Relapse free survival of patients according to HSP90 overexpression (Song et al., 2010).

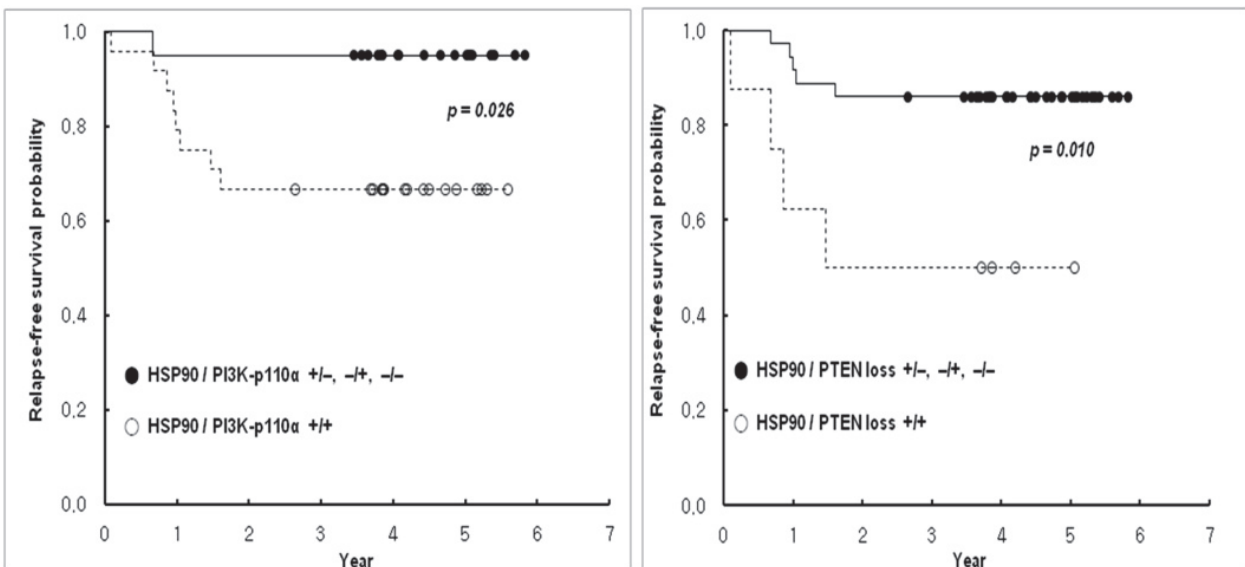


Fig. 8. Relapse free survival of patients with HER-2 overexpression (Song et al., 2010).

4. Epigenetic modulation of HER-2 signlaing: Histone deacetylase inhibition

Histone deacetylase inhibitors (HDIs) are capable of modifying gene expression without directly interacting with DNA by affecting the acetylation state of DNA-associated proteins, as well as other proteins.

We previously reported that HER-2 activated cells were preferentially radiosensitized by LBH589, the cinnamyl hydroxamic acid analogue panHDAC inhibitor compared to the effect of TSA or SK7041 at iso-effective concentrations and that this was associated with down-regulation of HER-2 signaling of SKBR-3 cells (Fig.9, Kim et al., 2009).

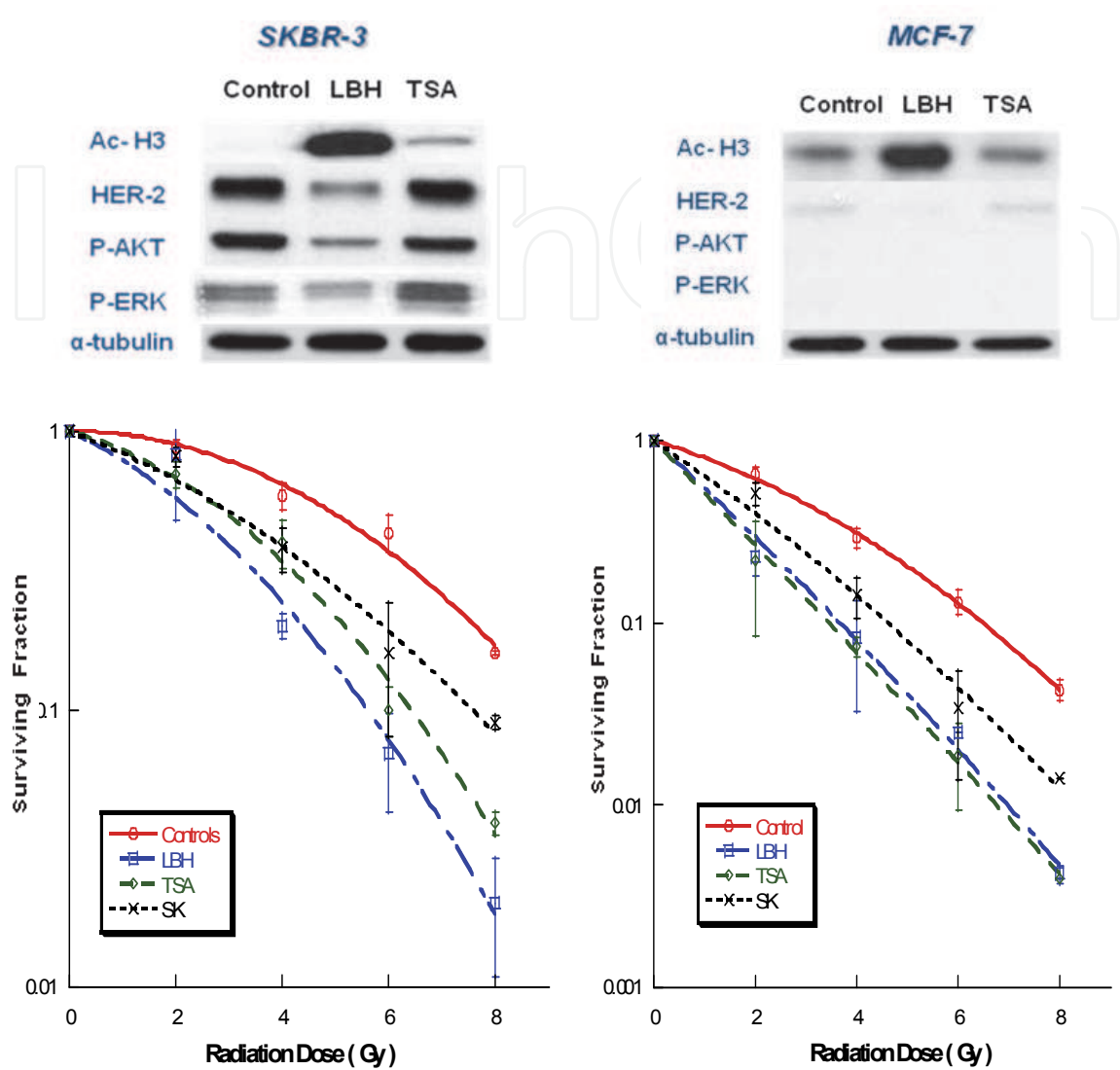


Fig. 9. LBH589 preferentially radiosensitizes breast cancer cells with HER-2 amplification (Kim et al., 2009).

The acetylation level of HSP90 and the relative inhibition of HDAC6 by the three different HDIs at iso-effective concentrations provided a mechanistic clue to explain this preferential radiosensitization by LBH589. Selective inhibition of HDAC6 led to acetylation of HSP90 resulting in ubiquitination and depletion of pro-survival client proteins including HER-2 and its downstream effectors. Specific inhibition of HDAC6 using RNAi increased acetylation of HSP 90 and attenuated the expression level of its client proteins such as p-AKT and p-ERK. This was associated with increased radiosensitivity of SKBR-3 cells (Fig.10, unpublished data).

The first evidence of non-nuclear and non-histone associated activity for a HDAC member came from the characterization of HDAC 6, one of the class IIB members. It possesses two deacetylase domains and zinc finger motif. The central part of this motif is similar to region found in BRAP (BRCA1-associated protein 2) and several ubiquitin-specific proteases. This

motif is also known as PAZ (polyubiquitin-associated zinc finger) due to its ubiquitin-binding ability. It has been implicated as a critical link between proteasome degradation and autophagy (Kawaguchi et al., 2003; Boyault et al., 200; Pandei et al., 2007). HDAC6 has been implicated in modulating receptor tyrosine kinase signaling. Increased acetylation of heat shock protein such as HSP90 by HDAC 6 inhibition may lead to mis-folding and degradation of survival associated client proteins such as oncogenic tyrosine kinases, RAF, and AKT (Bali et al., 2005). Stable knockdown of HDAC6 expression also causes a decrease platelet-derived growth factor receptor α (Kamera et al., 2008). Lee et al. recently found that HDAC6 deficient fibroblasts were more resistant to oncogenic Ras and HER2-dependent transformation, indicating a critical role of HDAC6 in oncogene-induced transformation (Lee et al., 2008). Thus, HDAC6 could be a good therapeutic target regulating critical cancer-relevant biologic functions. These reports and the current study suggest that HDAC 6 may be a useful target for overcoming therapeutic resistance to available HER2 inhibitors combined with radiation.

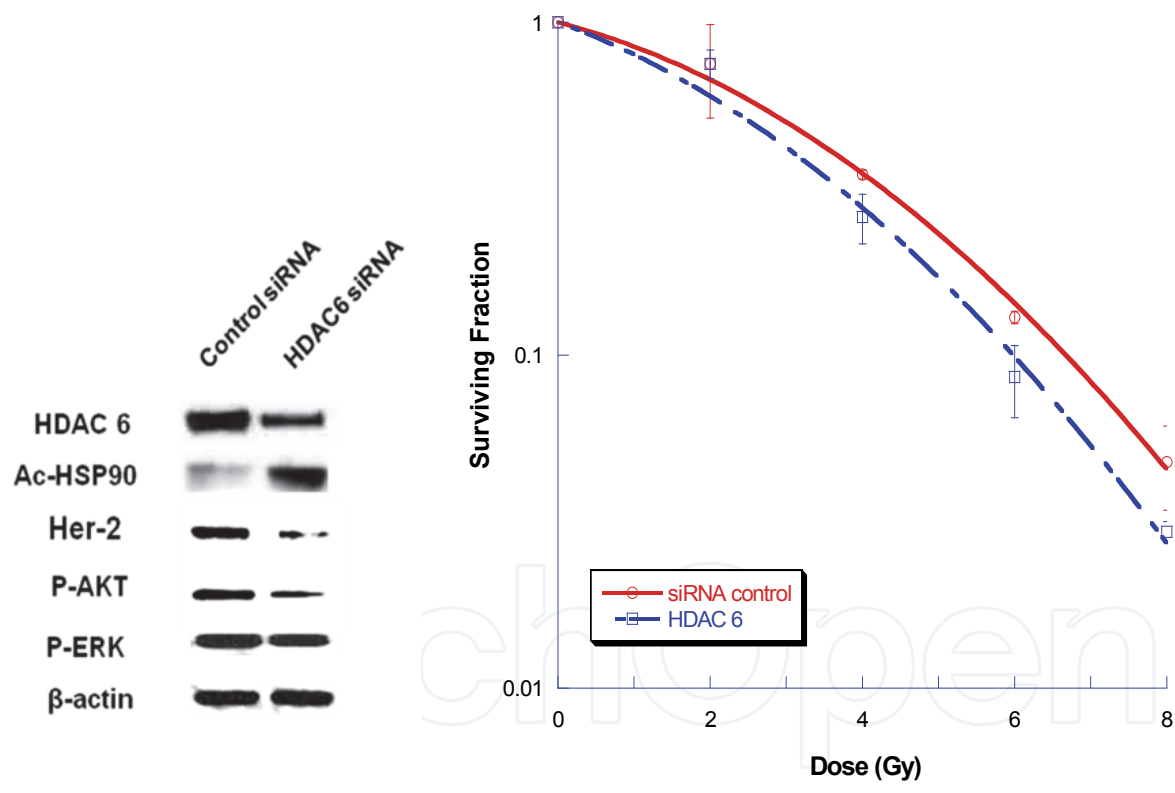


Fig. 10. Selective inhibition of HDAC6 radiosensitized SKBR-3 cells.

5. Conclusion

Identification of the prognostic significance of HER2 and its targeted therapy are the best examples of proof of concept (Hassa et al., 2005). A series of studies have shown solid preclinical and clinical evidences regarding the potential value of targeting HER-2 signaling to enhance the anti-tumor activity of ionizing radiation (Sartor et al., 2003; Sambade et al.,

2010). However, therapeutic resistance resulting from several factors including activation of downstream pathway or alternative survival pathways, as well as molecular resistance mechanisms, have emerged as an important issue in the clinic. Based on previous studies and our data, we propose that targeting downstream, ligand-independent modulation via HSP90 inhibitor, and epigenetic modulation via HDAC inhibitor could be an alternative approaches to tackle factors such as these that limit the therapeutic benefit of HER-2 targeted therapy combined with radiation.

6. Acknowledgment

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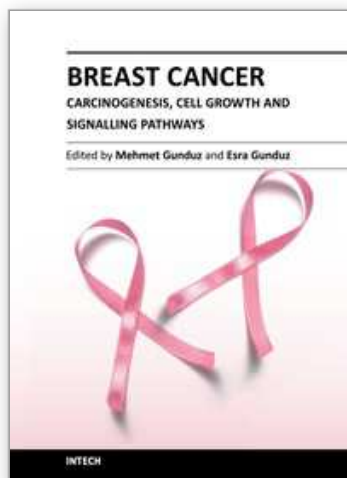
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